PROCESSES FOR THE PREPARATION OF CEPHALOSPORIN DERIVATIVES

BACKGROUND OF THE INVENTION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a 35 U.S.C. § 371 National Phase Entry Application from PCT/KR2004/002771, filed October 30, 2004, and designating the U.S.

~~Technical Field~~ 1. FIELD OF THE INVENTION

[0002] The present invention relates to a process for preparing cephalosporin derivatives, including cefprozil and its salt, using a 3-(Z)-propenyl cephem derivative stereospecifically prepared.

~~Background Art~~ 2. DESCRIPTION OF THE RELATED ART

[0003] 3-(Z)-propenyl cephem derivative is a compound useful as an intermediate for preparation of cefprozil which is an oral cephalosporin antibiotic. Various preparation processes thereof have been known.

[0004] WO93/16084 discloses a process for selectively separating a 3-(Z)-propenyl cephem compound by means of a hydrochloride, metal, or tertiary amine salt of 7-amino-3-(1-propen-1-yl)-3-cephem-carboxylic acid or by adsorption chromatography. However, there is a disadvantage in that separation and purification are cost-ineffective.

[0005] U.K. Patent No. 2,135,305 discloses a process for preparing cefprozil from a 4-hydroxyphenylglycine compound with a t-butoxycarbonyl-protected amino group and a cephem compound with a benzhydryl-protected carboxyl group. However, incorporation of a 3-propenyl group after acylation lowers reaction efficiency and

high-performance liquid chromatography is required for isomer separation, which render industrial application difficult.

[0006] U.S. Patent No. 4,727,070 discloses a technique of removing an E-isomer cefprozil from a mixture of Z/E cefprozil, which includes incorporating an active group such as sodium imidazolidinone into the mixture of Z/E cefprozil by reaction of the mixture of Z/E cefprozil with acetone, followed by deprotection. However, purification by chromatography incurs enormous costs.

[0007] In view of the above problems, Korean Patent Laid-Open Publication No. 2002-80838 discloses a process for preparing a 3-(Z)-propenyl cephem compound by reacting a phosphoranylidene cephem compound with acetaldehyde in a mixed solvent essentially consisting of ether in the presence of a base. According to a disclosure in this patent document, ether is essentially used. In this respect, in the case of using methylenechloride, tetrahydrofuran, etc., even when other reaction conditions, for example, reaction temperature, reaction duration, base, catalyst, and the like are adjusted, it is very difficult to adjust the content of the Z-isomer to more than 83%.

[0008] Korean Patent Laid-Open Publication No. 2002-69437 discloses a 4-hydroxyphenylglycine anhydride with a pivaloyl group, which is a compound useful as an intermediate for the 7-position of cefprozil, and a preparation process thereof.

SUMMARY OF THE INVENTION

[0009] The present invention provides a process for simply preparing a cephalosporin antibiotic in high yield and purity using a 3-(Z)-propenyl cephem

derivative stereospecifically prepared.

[0010] Therefore, the present invention provides a process for preparing a cephalosporin compound using a 3-(Z)-propenyl cephem derivative.

DETAILED DESCRIPTION OF THE INVENTION

~~Technical Goal of the Invention~~

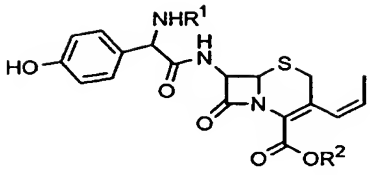
~~The present invention provides a process for simply preparing a cephalosporin antibiotic in high yield and purity using a 3-(Z)-propenyl cephem derivative stereospecifically prepared.~~

~~Therefore, the present invention provides a process for preparing a cephalosporin compound using a 3-(Z)-propenyl cephem derivative.~~

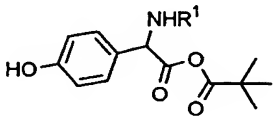
~~Disclosure of the Invention~~

[0011] According to an aspect of the present invention, there is provided a process for preparing a compound represented by the following formula 1 or its salt, which includes: reacting a compound represented by the following formula 4 with acetaldehyde in a mixed solvent including water, isopropanol, and methylenechloride in a volume ratio of 1:3-6:11-14 in the presence of a first base to stereospecifically prepare a compound represented by the following formulae 3 and reacting the compound of the formula 3 with an anhydrous compound represented by the following formula 2 in the presence of a second base:

<Formula 1>

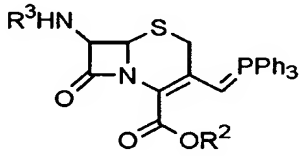


<Formula 2>



<Formula 3>

<Formula 4>



wherein R^1 is a hydrogen or an amino protecting group, R^2 is a hydrogen or a carboxyl protecting group, and R^3 is a hydrogen or an amino protecting group.

[0012] The salt of the compound of the formula 1 refers to a salt commonly known in the field of cephalosporin antibiotics, for example a hydrate or an acid addition salt.

[0013] As used herein, the term "stereospecific compound" refers to a mixed compound (e.g., compound of the formula 1 or 3) composed of a Z-isomer (or cis-isomer) and an E-isomer (or a trans-isomer) in a ratio of about 89-94% to about 6-11%, i.e., a compound composed of a Z-isomer and an E-isomer in a ratio of about

8.1-15.7:1.0. In this respect, the term "stereospecific preparation process" refers to a process for preparing the "sterespecific compound".

[0014] The carboxyl protecting group and the amino protecting group may be protecting groups commonly used in synthesis of cephalosporin antibiotics. Examples of the carboxyl protecting group include allyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, triphenylmethyl, and diphenylmethyl, and examples of the amino protecting group include 4-methoxybenzyl, formyl, acetyl, benzyl, benzylidene, diphenylmethyl, triphenylmethyl, trichloroethoxycarbonyl, t-butoxycarbonyl, methylacetoacetate, ethylacetoacetate, and 2-ethoxycarbonyl-1-methylvinyl. Preferably, the carboxyl protecting group of R^2 and the amino protecting group of R^3 are respectively 4-methoxybenzyl and benzylcarbonyl which are commercially available. Preferably, the amino protecting group of R^1 is a protecting group that can be easily removed in the presence of an acid.

[0015] According to the preparation process of the present invention, when the reaction is performed in the mixed solvent including water, isopropanol, and methylenechloride in a volume ratio of 1:3-6:11-14, the compound of the formula 3 can be prepared stereospecifically, i.e., so that a Z-isomer and an E-isomer of the compound of the formula 3 are in a ratio of about 8.1-15.7:1.0 which can be seen from Table 1 of the following Examples, and the compounds of the formulae 1 and 3 can be prepared in high yield and purity. In particular, when the volume ratio of water, isopropanol, and methylenechloride in the mixed solvent is 1:4:12, the Z/E isomers with high ratio of Z/E can be obtained in high yield.

[0016] In preparation of the compound of the formula 3, the mixed solvent may be used in an amount of about 5-20 times by weight, and preferably about 10-15 times by weight, based on the compound of the formula 4. Acetaldehyde may be used in an amount of about 5-30 equivalents (eq.), and preferably about 10-15 eq., based on 1 eq. of the compound of the formula 4. The preparation of the compound of the formula 3 may be performed at a temperature of about –20 to -10℃ for about 2 to 20 hours, and preferably about 10 to 15 hours.

[0017] The compound of the formula 4 can be prepared according to a known method (e.g., Korean Patent Laid-Open Publication No. 2002-80838). That is, the compound of the formula 4 can be prepared by reacting a 3-halomethyl cephem compound represented by the following formula 5 with triphenylphosphine to obtain a phosphonium salt, followed by treatment with a third base such as sodium hydroxide or sodium carbonate:

<Formula 5>

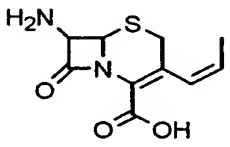
wherein R^2 and R^3 are as defined in the above and X is a halogen.

[0018] The preparation of the compound of the formula 4 and the preparation of the compound of the formula 3 can be performed by one-pot reaction without separately separating the compound of the formula 4. In this case, since the base used in the preparation of the compound of the formula 4 remains in a reaction solution, there is no need to further add a base in a subsequent process, i.e., in the

preparation of the compound of the formula 3, which simplifies preparation processes.

[0019] The compound of the formula 3 can be converted to 7-amino-3-[propen-1-yl]-3-cephem-4-carboxyl acid represented by the following formula 6 by common protecting group removal:

<Formula 6>



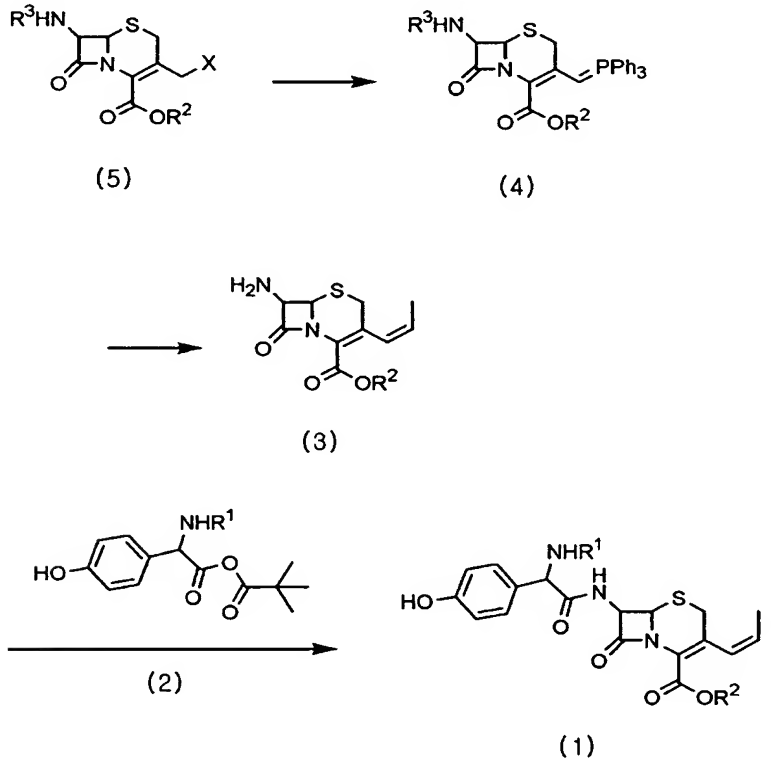
[0020] The compound of the formula 2 can be prepared according to a known method (Korean Patent Laid-Open Publication No. 2002-69437).

[0021] Preferably, the compound of the formula 2 is used in an amount of 1 to 3 eq., and preferably 1.1 to 1.5 eq., based on 1 eq. of the compound of the formula 3. Preferably, the reaction of the compound of the formula 2 with the compound of the formula 3 is performed in a mixed solvent of water with an organic solvent selected from the group consisting of diemethylsulfoxide, dimethylformamide, diemethylacetamide, 1,4-dioxane, acetonitrile, dichloromethane, and a mixture thereof. At this time, it is preferred that the content of water in the mixed solvent is 0.05 to 0.3 parts by weight, and preferably 0.1 to 0.2 parts by weight, based on 1 part by weight of the organic solvent. The reaction can be performed at a temperature of -50 to -20℃, preferably -40 to -30℃, for 1 to 4 hours, preferably 1.5 to 2.5 hours.

[0022] Examples of the second base that can be used in the reaction of the compound of the formula 2 with the compound of the formula 3 include N-methylmorpholine, triethylamine, diethylamine, n-tributylamine, N,N-dimethylaniline, and pyridine. Among them, triethylamine is preferred. Preferably, the second base is used in an amount of about 1.0 to 2.5 eq., preferably 1.1 to 1.5 eq., based on 1 eq. of the compound of the formula 2.

[0023] The entire preparation processes of the present invention can be expressed by the following reaction scheme 1:

<Reaction Scheme 1>



~~Effect of the Invetion~~

~~According to the present invention, cephalosporin antibiotics, including~~

~~cefprozil and its salt, can be easily prepared in high yield and purity using 3-(Z)-propenyl cephem derivative stereospecifically prepared.~~

~~BEST MODE FOR CARRYING OUT THE INVENTION~~

[0024] Hereinafter, the present invention will be described more specifically by Examples. However, the following Examples are provided only for illustrations and thus the present invention is not limited to or by them.

[0025] Example 1: Preparation of 7-phenylacetamido-3-[propen-1-yl]-3-cephem-4-carboxylic acid/p-methoxybenzyl ester

[0026] 16 g of sodium iodide and 28 g of triphenylphosphine were added to a reactor containing 50g (102.7mmol) of 3-chloromethyl-7-phenylacetamido-3-[propen-1-yl]-3-cephem-4-carboxylic acid p-methoxybenzyl ester. 400 ml of methylenechloride was added thereto and stirred at 20℃ for 2 hours. After phase separation, 200 ml of a 20% sodium hydroxide solution was dropwise added to an obtained organic layer and stirred at 10℃ for 30 minutes. After separation of an organic layer, a phosphoranylidene solution was obtained.

[0027] 200 ml of methylenechloride, 200 ml of isopropanol, and 50 ml of water were added to the phosphoranylidene solution and cooled to -20℃. 100 ml of acetaldehyde was dropwise added thereto and stirred for 20 hours. 30% potassium thiosulfuric acid was dropwise added and stirred for 30 minutes to separate an organic layer. 200 ml of isopropanol was dropwise added to the obtained organic layer, concentrated to produce a crystal, cooled to 0℃, and stirred for 2 hours to

precipitate a solid. The solid was filtered and dried in vacuum to give 42.3g (88.4mmol, yield 86%, Z/E=10.1/1) of the titled compound as a white solid.

H-NMR(δ , DMSO-d_6): 1.52(3Hx10.1/11.1, d, (Z)-CH_3), 1.73(3Hx1.0/11.1, (E)-CH_3), 3.36-3.68(4H, m, phCH_2, C-2), 3.75(3H, S, -OCH_3), 5.06-5.24(3H, m, CO_2-CH_2, C-6), 5.52-5.69(2H, d, -CH=CH(CH_3), 6.06(1H, d, -CH=CH(CH_3), C-7), 6.91(2H, d, ph), 7.19-7.62(7.19-7.62(7H, m, ph)

[0028] Example 2: Preparation of 7-amino-3-[propen-1-yl]-3-cephem-4-carboxylic acid

[0029] 22.8 g of phosphorous pentachloride, 150 ml of methylenechloride, and 8.88 ml of pyridine were added to a 20℃ reactor and stirred for 30 minutes. 30 g (62.6 mmol) of the 7-phenylacetamido-3-[propen-1-yl]-3-cephem-4-carboxylic acid p-methoxybenzyl ester prepared in Example 1 was dropwise added thereto, stirred for 2 hours, and cooled to -10℃. The reaction mixture was stirred for 2 hours after addition of 30 ml of 1,2-propanediol and then for 2 hours after addition of 120 ml of cresol. 200 ml of distilled water was dropwise added to the reaction solution and stirred for 1 hour. After phase separation, an aqueous layer was sent to a crystallization bath and an organic layer was extracted with 300 ml of 2N HCl and then the extract was sent to the crystallization bath. 200 ml of a 30% sodium hydroxide solution was dropwise added to the crystallization bath for crystallization and cooled to 0℃ to precipitate a solid. The solid was filtered and dried in vacuum to give 12g (50mmol, yield 80%, Z/E=10.1/1) of the titled compound as a beige solid.

H-NMR(δ , D_2O+NaHCO3): 1.69 and 1.88(3H, each, d, 6.0Hz, -CH=CH-CH_3), 3.38 and 3.72(2H, Abq, 17Hz, H-2), 5.18(1H, d, 5.0Hz, H-6), 5.51(1H, d, H-7), 5.8(1H, m, -CH=CH-CH_3), 6.06(1H, d, 11Hz, -CH=CH-CH_3)

[0030] Example 3: Preparation of 7-[2-amino-2-(4-hydroxyphenyl)acetamido]-3-[propen-1-yl]-3-cephem-4-carboxylic acid (cefprozil)

Step A

[0031] 75g (0.247mol) of potassium (2-ethoxycarbonyl-1-methyl-vinylamino)-(4-hydroxyphenyl)-acetate, 100 ml of dimethylformamide, and 10 ml of pyridine were added to a reactor and a mixed solution of 35 ml of pivaloyl chloride and 200 ml of methylenechloride was dropwide added thereto. The reaction mixture was stirred at -30℃ for 2 hours.

Step B

[0032] The reaction solution obtained in step A was cooled to -40℃ and then a solution obtained by dissolving 50g (0.208mol) of the 7-amino-3-[propen-1-yl]-3-cephem-4-carboxylic acid prepared in Example 2 in 200 ml of methylenechloride, 50 ml of water, and 6.5 g of triethylamine was slowly dropwise added thereto for 1 hour.

[0033] Then, the resultant solution was incubated at the same temperature for 2 hours and set to a temperature of 0℃ to obtain an insoluble solid. After the insoluble solid was filtered, a filtrate was sent to a reactor. 100 ml of 6N HCl was added thereto and stirred for 1 hour. The reaction solution was set to a pH of 3.2 by

addition of 10% NaOH, stirred at 0℃ for 2 hours, and filtered to give 68.9g (0.177mol, 85%) of the titled compound as a white solid.

H-NMR(δ , D_2O-d_2) : 1.65(3H, d, 8.6Hz, -CH=CHCH_3(cis)), 1.81(0.21H, d, 8.6Hz, -CH=CHCH_3(trans)), 3.22(1H, d, 18Hz, 2-H), 3.55(1H. d. 18Hz, 2-H), 5.15(1H, d, 4.6Hz, 6-H), 5.66(1H, d, 4.6Hz, 7-H), 5.75(1H, m, vinyl-H), 5.96(1H, m, vinyl-H), 6.91(2H, d, 8.0Hz, phenyl-H), 7.38(2H, d, 8.0Hz, phenyl-H)

[0034] Examples 4 and 5

[0035] 7-phenylacetamido-3-[propen-1-yl]-3-cephem-4-carboxylic acid p-methoxy -benzyl ester was prepared in the same manner as in Example 1 except that the volume ratio of methylenechloride, isopropanol, and water was as listed in Table 1 below. The yields and Z/E isomer ratios of the compounds of Examples 1, 4, and 5 are summarized in Table 1 below.

Table 1

Section	Methylenechloride (A) (ml)	Isopropanol (B) (ml)	Water (C) (ml)	Solvent ratio (A:B:C)	Yield (%)	Z/E isomer ratio
Example 4	150	150	50	11:3:1	83	8.9/1
Example 1	200	200	50	12:4:1	86	10.1/1
Example 5	300	300	50	14:6:1	85	9.1/1

[0036] As seen from Table 1, when a mixed solvent including methylenechloride, isopropanol, and water is used according to a solvent ratio as defined in the present invention, a 3-propenyl cephem compound of formula 3 can be stereospecifically prepared in high yield. In particular, when the volume ratio of methylenechloride,

isopropanol, and water was 12:4:1, the most excellent results were obtained in terms of yield and purity.

[0037] According to the present invention, cephalosporin antibiotics, including cefprozil and its salt, can be easily prepared in high yield and purity using a 3-(Z)-propenyl cephem derivative stereospecifically prepared.

[0038] While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit and scope of the present invention as defined by the following claims.